PALLADIUM-CATALYZED CARBOAMINATION: A KEY REACTION TO EXPLORE 3D DIVERSITY

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Introduction:

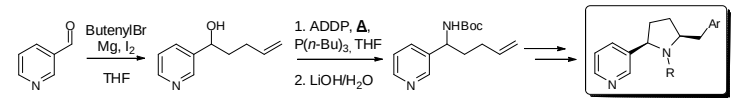
The European Lead Factory (ELF) is a pan-European platform which was set up to foster drug discovery in Europe.[1] In this 5-year programme, academic researchers from prestigious Universities and European CRO SME's have joined their efforts to assemble a new screening collection of 200 000 compounds based on innovative scaffolds. For this purpose, scientists at the University of Leeds identified the palladium catalyzed carboamination of γ-(*N*-protected) alkenes with aryl bromides as a powerful reaction to gain access to the biologically relevant pyrrolidine core.[2] After optimization and validation, this chemistry was transferred to Edelris' scientists for up-scaling and library production.

1. Up-scaling of key intermediates

Scientists at the University of Leeds devised and validated a route to the two γ-(*N*-Boc-amino) alkenes key intermediates (**Library-1** and **Library-2**), however, only on a limited scale. The goal for the EDELRIS-team is to quickly (within ~2 months from project hand-over) be able to deliver the final 5-600 compound library. In order to comply with certain criteria, such as reaction scale and number of final compounds, some parameters had to be revised during the up-scaling and production phases, e.g.: purification, reaction concentration, catalyst loading, safety, costs of reagents, just to mention a few.

The linear γ-(*N*-Boc-amino) alkene key intermediates for the two pyrrolidine-based libraries could be obtained on a multigram scale (as shown below) and in only a few steps from commercially available starting materials.

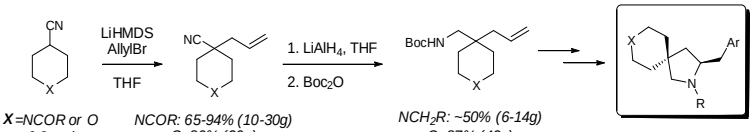
Library-1



0.2 mol (20g) — *86% (26g)* — *66% (21g)*

Δ=$EtO_2CCONHBoc$

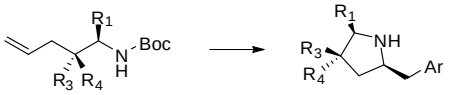
Library-2



X=*NCOR or O* *0.3 mol* — *NCOR: 65-94% (10-30g)* *O: 89% (30g)* — NCH_2R: *~50% (6-14g)* *O: 87% (42g)*

2. First diversification: palladium-catalyzed carboamination

The core pyrrolidine scaffolds were set up by an intramolecular Pd-catalyzed carboamination reaction on the above shown intermediates. Depending on the last-stage production reagents, the reactivity of the different subfamily scaffolds could vary and should be assessed in order to maximize the **P**roduction **S**uccess **R**ate (P.S.R.). Therefore, a preliminary screening on a set of preselected arylbromides was carried out on a 0.15 mmol scale. This experimental refining of the enumerated selection of arylbromides gave us a set of arylbromides which were anticipated to work on a 12 mmol scale (non-exhaustive examples are shown below).



Conditions:
a) Ar-Br, $Pd(OAc)_2$, dpePhos
Cs_2CO_3, dioxane, 100°C.
b) TFA, DCM

Ph-Br	Yield
2-CN	52%[a]
3-OMe	59%[a]
4-SO_2Me	66%[b]

pyridines	Yield
2-Br, 5-F	58%[b]
3-Br, 5-OMe	63%[b]
3-Br, 6-NHAc	87%[b]

Misc. Ar-Br	Yield
5-Br benzofuran	59%[a]
5-Br indole	Failed[a]
2-Br thiazole	Failed[a]

Notes: Representative isolated yields are indicated for either Library-1 (a) or Library-2 (b). Diastereomeric ratios were > 20:1 (Library-1)

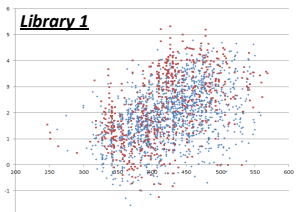
3. Production phase

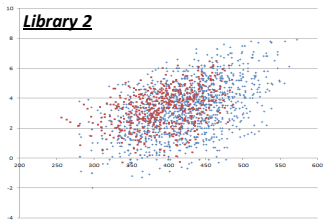
To access the final library compounds the last synthetic step involves a high throughput decoration of the pyrrolidine amino-group, using the reaction types shown below. To increase the P.S.R. the reactivity of the used electrophiles was continuously assessed.

Reaction type	Reaction conditions
Peptide coupling	RCOOH, TBTU, DIPEA, DMF
Reductive Amination	RCHO, STAB, AcOH, DMF or DCE
Misc. Electrophilic additions	R-SO2Cl or ROCOCl, DIPEA, DMF
Carbamate formation	RNCO, DMF

4. Results

607 compounds (P.S.R. 82%, A.Y. 33%)[4] and 598 compounds (P.S.R. 79%, A.Y. 38%) were produced respectively for Library-1 and Library-2, meeting the ELF quality and quantity standards (purity >85%, >5mg). Furthermore, the required diversity was not jeopardized, as all compounds have a similarity factor below 0.85 as defined by the Lead Discovery Centre and EFPIA[5] criteria.





Note: cLogP represented as a function of MW of the produced (•) *vs.* enumerated compounds (•)

Process & Purification

To be able to deliver at such high throughput rate, the production process has been revised, inspired by the Lean Sigma approach and its tools : 5S, SMED etc.

Examples of guidelines that have been set up:
- All library compounds are purified by mass-directed preparative LCMS.
- Solvents used for the last diversification step have to be suitable for direct loading onto the preparative LCMS column.
- Compound Data are automatically recorded from reaction enumeration to final Quality Control (QC).

Examples of implemented solutions are:
- Format Standardization from reaction set-up to purification.
- Transposition of the retention time from 3.5min UPLC/MS analysis to a 10min compound-focused preparative HPLC/MS purification.

Conclusion

The production of two novel and highly functionalized pyrrolidine chemical libraries has been successfully achieved. Owing to the production process that we have developed at EDELRIS, we were able to deliver these two attractive libraries in full compliance with the quality standards defined by the ELF-consortium, and in respect of the defined timelines (<2months). The ELF project is only in its second year, and we are continuing the adventure by working further towards the development and production of innovative chemical libraries, in respect of the same quality and timeline standards as shown above.

Acknowledgment

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1) The European Lead Factory: Game Changing for Innovative Medicine. Ton Rijnders, Dimitrios Tzalis, Eckhard Ottow. http://www.europeanleadfactory.eu
2) a) Bertrand, Myra Beaudoin; Wolfe, John P. Tetrahedron (2005), 61(26), 6447-6459. b) Bertrand, Myra Beaudoin; Wolfe, John P. Organic Letters (2007), 9(16), 3073-3075.
3) Berree, F.; Michelot, G.; Le Corre, M. Tetrahedron Lett. 1998, 39, 8275-8276.
4) A.Y. = Average Yield
5) EFPIA = European Federation of Pharmaceutical Industries and Associations

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